

REMARKS**Interview request**

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant RCE response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133.

Status of the Claims*Pending claims*

Claims 8 to 28, 30, 31, 33 to 41, 44, 46, 48 to 59, 64 and 66 to 72, are pending. Claims 15 to 18, 59, 69 and 70 are withdrawn from consideration. Thus, claims 8 to 14, 19 to 28, 30, 31, 33 to 41, 44, 46, 48 to 58, 64, 66 to 68, 71 and 72, are pending and under consideration.

Allowable subject matter

Applicants thank the Examiner for noting that claims 12, 14, 20 to 22, 41, 44, 46, 48, 49, 54, 55, 58 and 66, appear allowable over the prior art of record but are objected to for depending on rejected claims.

Claims added in the instant amendment

In the present response, claims 73 to 78 are added. Accordingly, after entry of the instant amendment, claims 8 to 14, 19 to 28, 30, 31, 33 to 41, 44, 46, 48 to 58, 64, 66 to 68, 71 and 72 to 78 will be pending and under examination.

Outstanding Objections and Rejections

Claims 12, 50, 54 and 56 are objected to. Claims 67, 68, 71 and 72, are rejected under 35 U.S.C. §112, second paragraph. Claims 8 to 11, 13, 19, 23 to 28, 30, 31, 33 to 40, 50 to 53, 56, 57, 64, 67, 68, 71 and 72, remain rejected under 35 USC §103(a) as allegedly unpatentable over Cheng, et al., U.S. Patent No. 5,939,303, filed November 6, 1996, issued August 17, 1999 (hereinafter "Cheng"), in view of Greiner et al. (1993) Archives of Biochemistry and Biophysics 303:107-113 (hereinafter "Greiner"). Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the claim amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Accordingly, no new matter has been added by the instant amendments.

Specification

The instant amendment removes the last remaining hyperlink improperly embedded in the specification as filed, as discussed in detail in paragraph 2, page 2, of the OA.

Objections to the Claims

The Office objected to claims 12, 50 and 56, as discussed in detail in paragraph 4, page 3, of the OA; objected to claim 54, as discussed in detail in paragraph 5, page 3, of the OA. The instant amendment addresses this issue.

Issues under 35 U.S.C. §112, second paragraph

Claims 67, 68, 71 and 72 stand rejected as allegedly failing to comply with the requirements of 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, as set forth in detail in paragraphs 7 and 8, pages 3 to 4 (for claims 67, 68, 71 and 72) of the OA. The instant amendment addresses these issues.

Issues under 35 U.S.C. §103(a)Cheng in view of Greiner

Claims 8 to 11, 13, 19, 23 to 28, 30, 31, 33 to 40, 50 to 53, 56, 57, 64, 67, 68, 71 and 72, remain rejected under 35 USC §103(a) as allegedly unpatentable over Cheng, et al., U.S. Patent No. 5,939,303, filed November 6, 1996, issued August 17, 1999 (hereinafter “Cheng”), in view of Greiner et al. (1993) Archives of Biochemistry and Biophysics 303:107-113 (hereinafter “Greiner”), for reasons set forth in detail in paragraphs 12 to 14, pages 5 to 8, of the OA.

Warden and Wodzinski

Before discussing these issues in detail, Applicants apologize for the confusion regarding submission of the Warden, et al. (1962) “Action of antibiotics in stimulating growth of poultry.

Effect of *E. coli* and fecal preparations,” Poultry Sci. 41:725 (hereinafter “Warden”) and Wodzinski and Ullah (1996) “Phytase” Advances in Applied Microbiol. 42:263-302 (hereinafter “Wodzinski”) references, in which they inadvertently stated that these two references were submitted in a supplementary information disclosure statement (IDS) attached to their last response.

Warden is attached herein in a supplementary IDS filed with this response. Wodzinski was presented in an IDS submitted June 14, 2005 (as item 24, on sheet two, of that IDS; and considered (initialed) by Examiner on January 04, 2006); however, for the Office’s convenience, another copy of the Wodzinski review is attached herein.

Golovan, et al. (2000) Can. J. Microbio. 46:59-71 (hereinafter “Golovan”) was presented in an IDS submitted February 12, 2003; and for the Office’s convenience another copy is attached herein.

Nelson, et al., (1971) “Effect of Supplemental [*Aspergillus*] Phytase on the Utilization of Phytate Phosphorus by Chicks”, Journal of Nutrition Vol. 101 No. 10 October 1971, pp. 1289-1293, is attached herein in a supplementary IDS filed with this response.

Cheng in view of Greiner and the state of the art

Applicants thank the Office for clarifying that the obviousness rejection is based not just on Cheng and Greiner alone, but on the combination of Cheng and Greiner along with the knowledge of one of ordinary skill in the art (see, e.g., page 6, second sentence of the second paragraph of section 14, of the OA).

However, at the time of the invention the knowledge of one of ordinary skill in the art included art that teaches away from the invention as currently claimed:

Teaching away and difficulties in manufacturing phytase

The (amended) claimed invention encompasses feeds and foods comprising a phytase made by a method comprising providing a phytase-encoding nucleic acid isolated from an *E. coli*, or a synthetic or recombinant form of the phytase-encoding nucleic acid isolated from the *E. coli*, and expressing the nucleic acid under conditions which allow expression of the phytase. One of the unmet challenges in the industry before this invention was to economically provide sufficient quantities of isolated, synthetic or recombinant forms of phytase for the enzyme’s inclusion in a feed or a food.

Before this invention it had been known that crude preparations of *E. coli* – lysed and dried and/or lyophilized cultured *E. coli* cells (the *E. coli* was initially isolated from chicken fecal matter) – when fed to phosphorus deficient growing chicks allowed normal growth and bone development; see e.g. Warden, et al. (1962) “Action of antibiotics in stimulating growth of poultry. Effect of *E. coli* and fecal preparations,” Poultry Sci. 41:725 (submitted in the supplementary IDS attached herein). Warden suggested that the active agent “essentially increasing the phosphorus content of the ration” in the crude *E. coli* whole cell lysates fed to the growing chicks might, or might not, be enzymatic in nature, e.g., a phytase or similar enzymes:

... In these studies, the results suggest the probability that dried *E. coli* cellular material *may* contain phytase or similar enzymes making previously unavailable phosphorus available to the bird. Basis for this explanation is the fact that birds responded in a similar manner to addition of available phosphorus, or to one percent of lysed *E. coli*, which did not essentially increase the phosphorus content of the ration. This *suggests* that the effect, therefore, *may be* enzymatic in nature. ... *On the other hand, part of the response observed from feeding lysed E. coli in the absence of available phosphorus could possibly be due to other properties provided by the bacterial preparation.* [emphasis added]

Please see page 730, right hand column, of Warden.

Furthermore, before this invention no one had produced sufficient quantities of isolated, synthetic or recombinant forms of phytase for inclusion in a food or a feed, particularly an economically viable commercial feed or food; see also Nelson, et al., (1971) “Effect of Supplemental [*Aspergillus*] Phytase on the Utilization of Phytate Phosphorus by Chicks”, Journal of Nutrition Vol. 101 No. 10 October 1971, pp. 1289-1293 (also submitted in the supplementary IDS attached herein).

As recently as 1996 (before the priority date of the instant application) experts in this field expressly dismissed bacteria as a source of phytase for use in a food or feed, see e.g., the review by Wodzinski, in particular – page 272, section B, entitled “Bacterial Sources”:

Phytase has been detected in *Aerobacter aerogenes* ..., *Bacillus subtilis* ..., *Escherichia coli* ..., *Pseudomonas* The only bacterial organism that produces extracellular phytase is *B. subtilis*. When phytase is produced by bacteria, the yields are low and the pH optimum is neutral to alkaline that precludes their use as feed additives. [emphasis added]

Thus, according to Wodzinski, as of 1996, experts in this field believed that when phytase is produced by bacteria – because the yields are low and the pH optimum is neutral to alkaline – use of an *E. coli* phytase as a feed additive is precluded.

Wodzinski provides a very detailed history of how difficult and costly it was to develop a fungal phytase for use in a food or feed (note: use of *E. coli* phytases was dismissed as impractical). For example, Wodzinski on page 264, lines 1 to 3 states: "[c]ommercialization [of phytase] was not possible until methods were available to develop and produce high yields of the enzyme in microbial culture or in plants." On page 266, section 3, Wodzinski states: "[t]he first concentrated effort to make phytase a commercial product started in 1962 ... in which approximately 12 man years were expended on the project." In brief, over 2000 organisms were screened for phytase activity, and an *A. niger* phytase was identified. Wodzinski concludes "[u]nfortunately, the yields of phytase at this time were not high enough to produce a product that would have to be increased, by one estimate, by about 250-fold just to break even" (please see the last paragraph of section 3, page 267).

Wodzinski also notes that in one effort it took 16 man years to isolate, characterize and sequence phytases made by an *A. niger* (please see the paragraph spanning pages 267 and 268, in section 4); and another group expended 40 man years to improve the yields of an *A. niger* (see the first sentence of section 5, page 268); and concluded that the full effort took about 68 man years (see the sentence spanning pages 268 and 269).

Wodzinski's detailed history of how difficult and costly it was to develop a fungal phytase for use in a food or feed further evidences the need in the industry to identify a phytase suitable for use in a feed or food, and also evidences the need in the industry to develop a means to economically make a microbial phytase in sufficient amounts for inclusion in a food or feed.

Golovan provides additional evidence that there was a long-felt need in the industry to identify a phytase suitable for use in a feed or food. Golovan published about two and a half years after the filing date of this application's priority document, which is August 13, 1997, for USSN 08/910,798, which issued on March 2, 1999, as USPN 5,876,997 (this application published as U.S. patent app. pub. no. 20030049815, on March 13, 2003). Thus, Golovan published their work having the benefit of this invention's specification.

As is made clear in their introduction (page 60), Golovan was motivated to do the work described in this paper to address the long-felt need in the industry to identify and characterize a phytase suitable for use in a feed or food. After giving a brief history of *E. coli* phytase research, Golovan concludes with "[t]he purpose of this investigation was to reexamine the catalytic properties of the acid phosphatase [a phytase] from *E. coli*, and to overproduce the enzyme for further biological and structural studies and to determine its suitability for industrial applications." Thus, Golovan illustrates that even two and a half years after the priority date of this application the public state of the art (at least as far as the scientific literature) was still searching for an appropriate phytase for use in foods or feeds (Golovan probably wasn't aware of any patent publications, including USPN 5,876,997 (not surprising for an academic at that time) – they certainly didn't cite Applicants' patent or any other patent in their extensive list of references, please note pages 69 to 71, of Golovan).

Accordingly because at the time of the invention the knowledge of one of ordinary skill in the art included art that expressly taught away from the currently claimed invention, the

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 12 (2007) recently addressed the importance of a teaching away in considering obviousness, noting "...when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious (citing *United States v. Adams*, 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966)).

The rejection is rebutted by secondary indicia of nonobviousness

Applicants respectfully aver that by submission of evidence of secondary indicia of nonobviousness they can overcome an obviousness rejection, even if, *arguendo*, the Patent Office has showed sufficient evidence of *prima facie* obviousness.

The secondary considerations are also essential components of the obviousness determination. See In re Emert, 124 F.3d 1458, 1462, 44 USPQ2d 1149, 1153 (Fed. Cir. 1997) ("Without Emert providing rebuttal evidence, this *prima facie* case of obviousness must stand."). This objective evidence of nonobviousness includes **copying, long felt but unsolved need**, failure of others, see Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966), **commercial success**, see In re Huang, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689-90 (Fed. Cir. 1996), unexpected results created by the claimed invention, unexpected properties of the claimed invention, see In re Mayne, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997); In re

Woodruff, 919 F.2d 1575, 1578, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990), licenses showing industry respect for the invention, see Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 USPQ2d 1294, 1297 (Fed. Cir. 1997); Pentec, Inc. v. Graphic Controls Corp., 776 F.2d 309, 316, 227 USPQ 766, 771 (Fed. Cir. 1985), and skepticism of skilled artisans before the invention, see In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

In re Rouffet, 47 U.S.P.Q.2D (BNA) at 1456.

Commercial success – long felt need - copying

Applicants have submitted sufficient evidence of secondary indicia of nonobviousness to rebut any possible *prima facie* case by submission of the declaration of Dr. Nelson Barton, a research and development scientist at Verenium (formerly Diversa) Corporation, the owner of this application, in a previous response. Applicants reiterate and expressly incorporate by reference all previous arguments, including Dr. Barton's Rule 132 declaration; however, to briefly summarize:

Dr. Barton declared that he believes that at the time of this invention there was a long-felt need in the food, agricultural feed and biotech industry for an invention such as that set forth in the pending claims, i.e., an invention comprising use of an *E. coli* phytase in a food or a feed. Dr. Barton declared that this long-felt need is evidenced by the commercial success of Diversa Corporation's PHYZYME® *E. coli* phytase feed enzyme, noting that Diversa Corporation was the first entity to make and market an *E. coli* phytase-comprising feed (in collaboration with its exclusive licensee; in the U.S. PHYZYME® phytase is available for sale through Danisco Animal Nutrition, Danisco A/S, Copenhagen, Denmark).

Dr. Barton declared that use of an *E. coli* phytase is at least in part responsible for the commercial success of the claimed feed and food supplement (the "nexus") – because *E. coli* phytases have unique properties (including a higher specific activity property) that distinguish them from phytases from other organisms, including other bacteria, they would be a better phytase enzyme to use in a food or feed – and it was the inventors of this invention that exploited this higher specific activity property and used an *E. coli* phytase in a food or feed:

6. ... While it was known in the art at the time of the invention that *E. coli* phytases have higher specific activity than phytases from other organisms, including other bacteria, it was this invention that for the first time realized and exploited this higher specific activity property and used an *E. coli* phytase in a food or feed.

7. Additionally, this invention was the first to realize that because *E. coli* phytases operate at a relatively acidic pH of between about pH of 4.5 to 5.5, and have a better activity in this pH range than phytases from other organisms, including other bacteria, they would be a better phytase enzyme to use in a food or feed (because the stomach environment is one of low pH, enzymes that maintain high activity in acidic conditions can be a preferred choice for use in a food or feed). While it was known in the art at the time of the invention that *E. coli* phytases operate at a relatively acidic pHs, it was this invention that for the first time realized and exploited this low pH (acidic) activity profile and used an *E. coli* phytase in a food or feed.

8. Furthermore, this invention was the first to realize that because *E. coli* phytases are substrate specific and are very active on phytate and not as active on other phosphate-containing compounds, they would be a better phytase enzyme to use in a food or feed. While it was known in the art at the time of the invention that *E. coli* phytases operate at a relatively acidic pHs, it was this invention that for the first time realized and exploited this substrate activity profile and used an *E. coli* phytase in a food or feed.

See paragraphs 6 to 8, pages 2 to 3, of Dr. Barton's expert declaration submitted July 11, 2006.

Dr. Barton declared that after the priority date of this application, other food and feed enzyme companies realized the value of this discovery and began to investigate the use *E. coli* phytases in feeds:

9. After the priority date of this application, other food and feed enzyme companies realized the value of this discovery and began to investigate the use *E. coli* phytases in feeds.

See paragraph 9, page 3, of Dr. Barton's expert declaration submitted July 11, 2006.

Dr. Barton summarized that it was this invention that for the first time used an *E. coli* phytase in a food or feed to result in a better phytase enzyme-supplemented product, for which there was a long-felt need at the time of the invention.

10. In summary, it was this invention that for the first time used an *E. coli* phytase in a food or feed to result in a better phytase enzyme-supplemented product, for which there was a long-felt need at the time of the invention.

The Office maintains that Dr. Barton's declaration does not provide sufficient secondary evidence to overcome a *prima facie* case of obviousness because, inter alia, the functional characteristics of *E. coli* phytases, e.g., their high activity in acidic conditions, were well known in

the art; and allegedly that only if the functional characteristics of *E. coli* phytases were not known would this evidence be relevant to a secondary indicia of nonobviousness; see e.g., the first full paragraph of page 9, of the office action of October 12, 2006, in particular, lines 5 to 11 of that paragraph.

Applicants respectfully maintain that the provided for declaration presenting the secondary indicia of nonobviousness elements of copying, commercial success and long-felt need remain relevant because this invention for the first time made a food or feed comprising an *E. coli* phytase. This invention for the first time describes feeds or foods comprising an *E. coli* phytase.

In conclusion, Applicants have provided objective evidence of nonobviousness, including long-felt need, copying and commercial success of the claimed food or feed. Applicants respectfully aver that this objective evidence of nonobviousness is sufficient to rebut a possible *prima facie* case of obviousness.

In view of the above remarks and referenced publications showing the art's teaching away from this claimed invention, and the evidence of secondary indicia of nonobviousness as set forth in Dr. Barton's expert declaration, Applicants submit that a *prima facie* case of obviousness has not been made, and alternatively, that they have rebutted any possible *prima facie* case of nonobviousness. Accordingly, the rejection under 35 U.S.C. §103(a) can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the objections to the claims, and the rejection of the pending claims under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §103(a). In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 564462001811. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 5133.

Dated: October 11, 2007

Respectfully submitted,

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